

# ADVERSE EVENT GRID RATES AND HISTORY

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Disclosures - \* O – VueCare Media

## FDA Study and Grid

- February 1978, FDA Investigational studies of IOL's
- 1982- Data pooled on 17 different IOL's from seven manufacturers (45,543 study cases and 8597 CORE cases)
- Publication Stark et al. Ophthalmology 1983, "The FDA Report on Intraocular Lenses"
- Used by FDA and ophthalmic devices panel and manufacturers as a historical control

# The FDA Report on Intraocular Lenses

WALTER J. STARK, MD, DAVID M. WORTHEN, MD, JACK T. HOLLADAY, MD, PATRICIA E. BATH, MD, MARY E. JACOBS, PhD,\* GEORGE C. MURRAY, PhD,\* ELEANOR T. MCGHEE,\* MAX W. TALBOTT, PhD,\* MELVIN D. SHIPP, OD,\* NANCY E. THOMAS, MD, ROGER W. BARNES,\* DANIEL W. C. BROWN, PhD,\* JORGE N. BUXTON, MD, ROBERT D. REINECKE, MD, CHANG-SHENG LAO, PhD,\* SCARLETT FISHER\*

**Abstract:** Clinical studies of intraocular lenses (IOLs) as investigational devices have been regulated in the United States by the Food and Drug Administration (FDA) since February 9, 1978. As of August 1982, data have been collected on more than one million IOLs implanted. During the last 12 months of the study, 409,000 IOLs were implanted. Visual acuity of 20/40 or better at one year after surgery was present in 85% of over 45,000 cases reviewed. Increasing patient age, surgical problems, postoperative complications, and adverse reactions were factors that reduced the visual acuity. The current trend in the USA is for implantation of the posterior chamber and anterior chamber IOLs. [Key words: cataract, intraocular lenses, pseudophakos, U.S. Food and Drug Administration (FDA).] *Ophthalmology* 90:311-317, 1983

Cataract is the second leading cause of existing blindness in the United States and, therefore, a significant public health problem. The use of intraocular lens (IOL) implantation at the time of cataract extraction has been increasing steadily since the early 1970s. In February 1978, national studies of IOLs were begun under investigational device exemption (IDE), approved by the FDA, to determine the safety and effectiveness of IOLs as a medical device for the correction of aphakia.<sup>1-3</sup>

The purpose of this report is to present information on the numbers, the types, and the current usage trends of the IOLs being implanted in the United States and to provide data on those lenses that have been reviewed by the Ophthalmic Device Section of the FDA Ophthalmic, Ear, Nose, Throat, and Dental Devices Panel of the Office of Medical Devices, and have been

recommended for premarket approval as being safe and effective.

## MATERIALS AND METHODS

Beginning February 9, 1978, all IOL patients in the United States were implanted by surgeons who were clinical investigators under an approved IDE. Cases were categorized as either "CORE" or "Adjunct Safety" depending on the frequency of postoperative reporting (Table 1). Data on a minimum of 500 CORE study cases followed for 12 to 14 months were required by the FDA before an IOL could be considered for premarket approval. One hundred completed CORE cases were required for any potentially significant modification of an existing IOL. Adverse reactions, sight-threatening complications, and surgical complications were reported by the physician to the manufacturer. Visual acuity results were provided at the standard reporting intervals. Satisfactorily completed premarket approval applications (PMAs) were reviewed in sequence. Some were delayed because of incomplete data.

Data submitted to the FDA from the manufacturers were analyzed for clinical significance by the Ophthalmic Device Section, an FDA Advisory Committee. In some cases additional information on complications, tracking

\* By invitation.

Presented at the Eighty-seventh Annual Meeting of the American Academy of Ophthalmology, San Francisco, October 30-November 5, 1982.

This is not an official report of the Food and Drug Administration. The opinions and statements contained in this article are those of the authors and may not reflect the views of the Food and Drug Administration.

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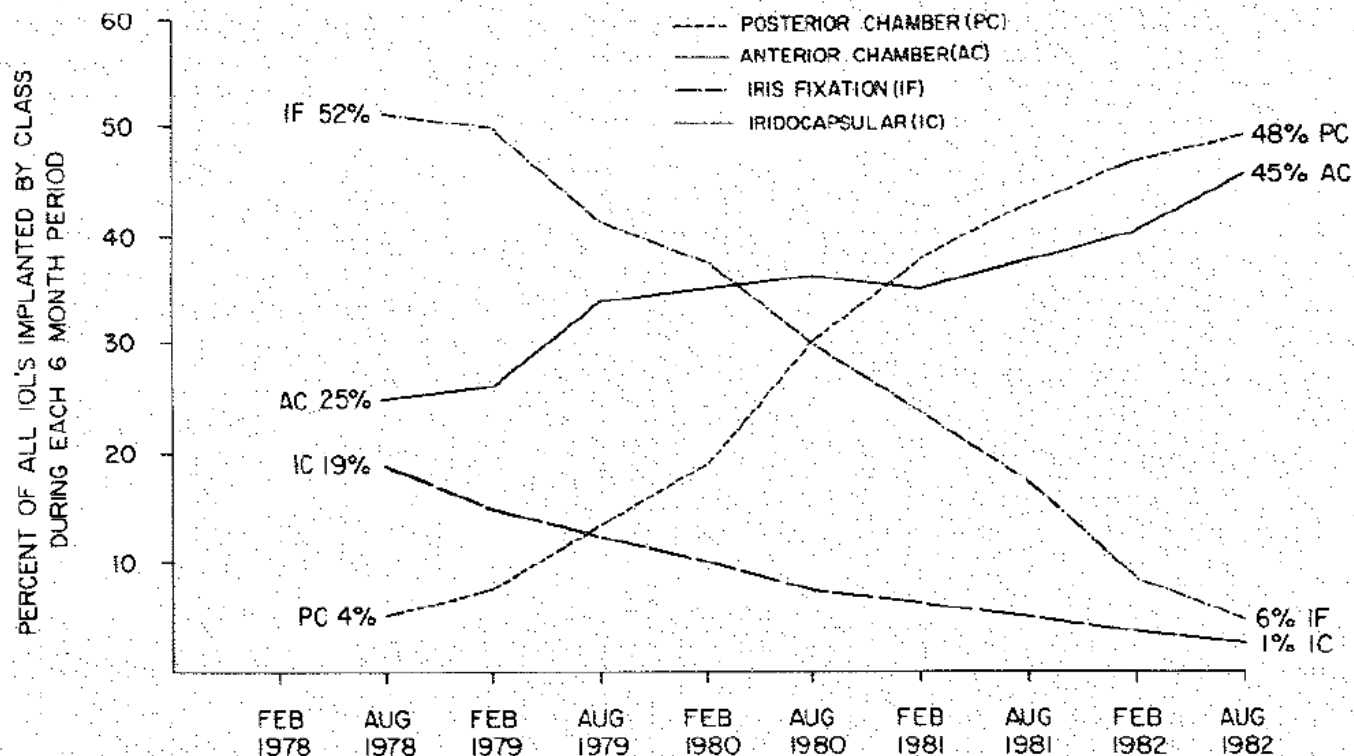
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Fig 2. Percentage of all intraocular lenses implanted by class for each six-month period.





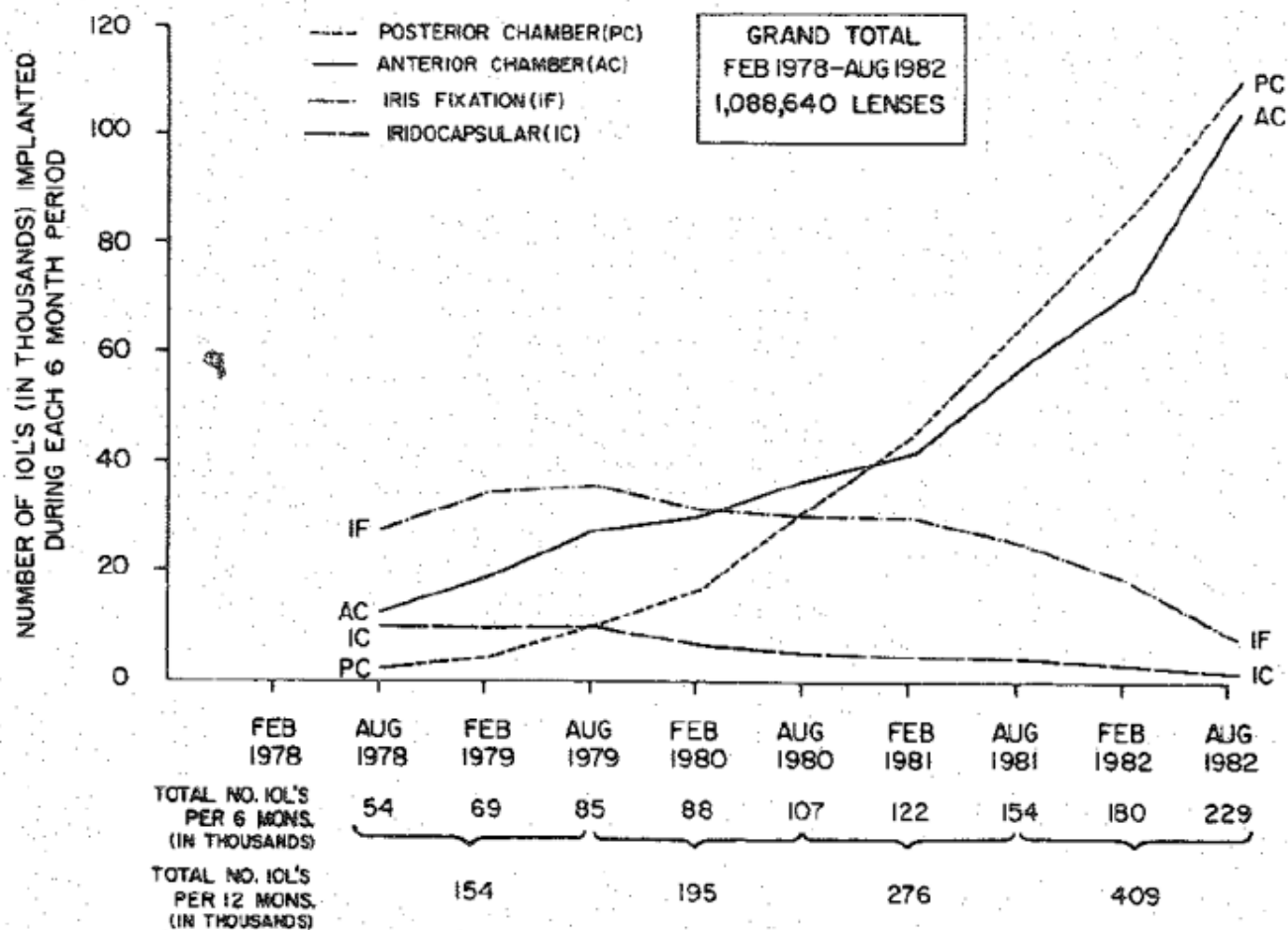
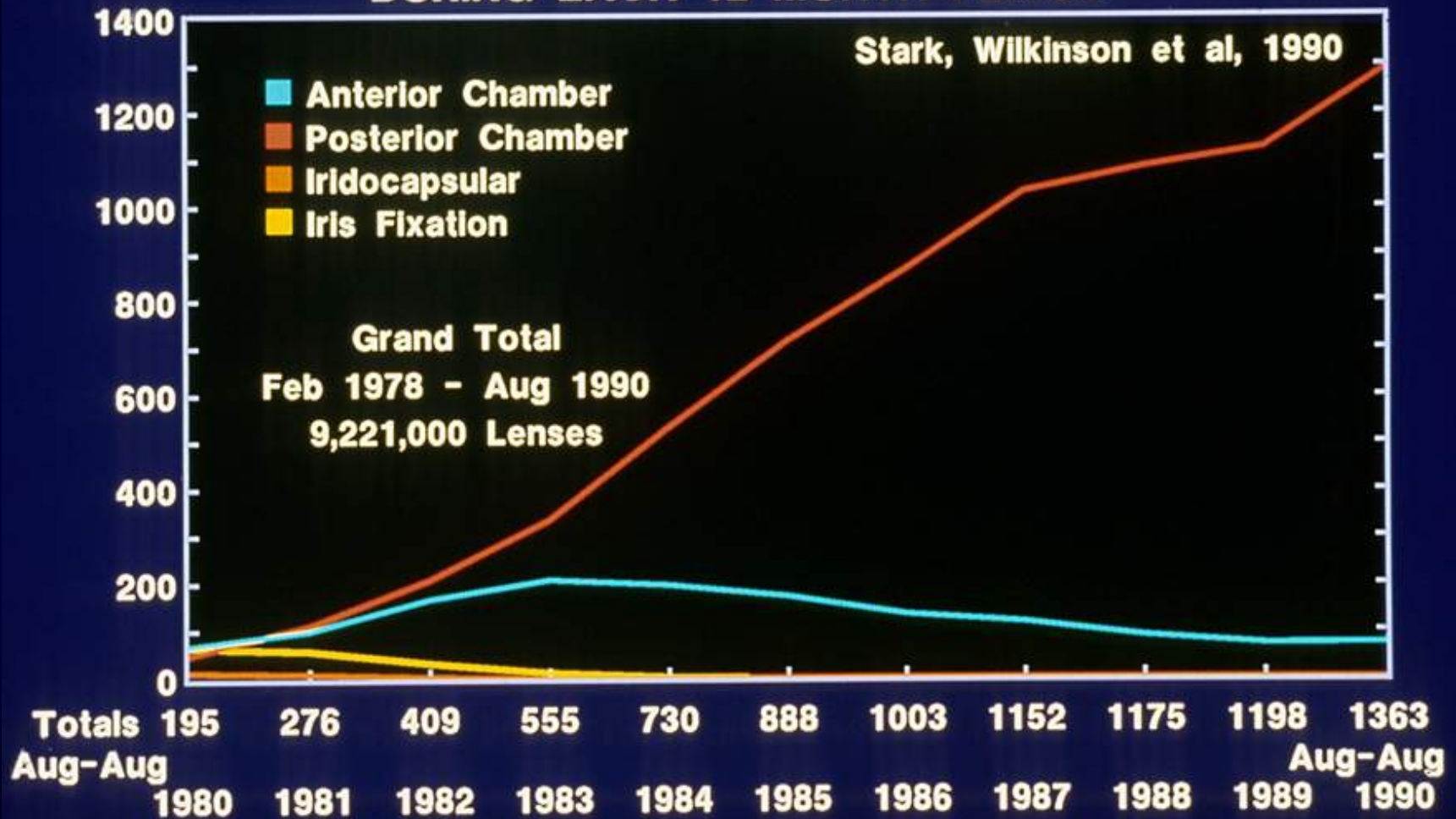
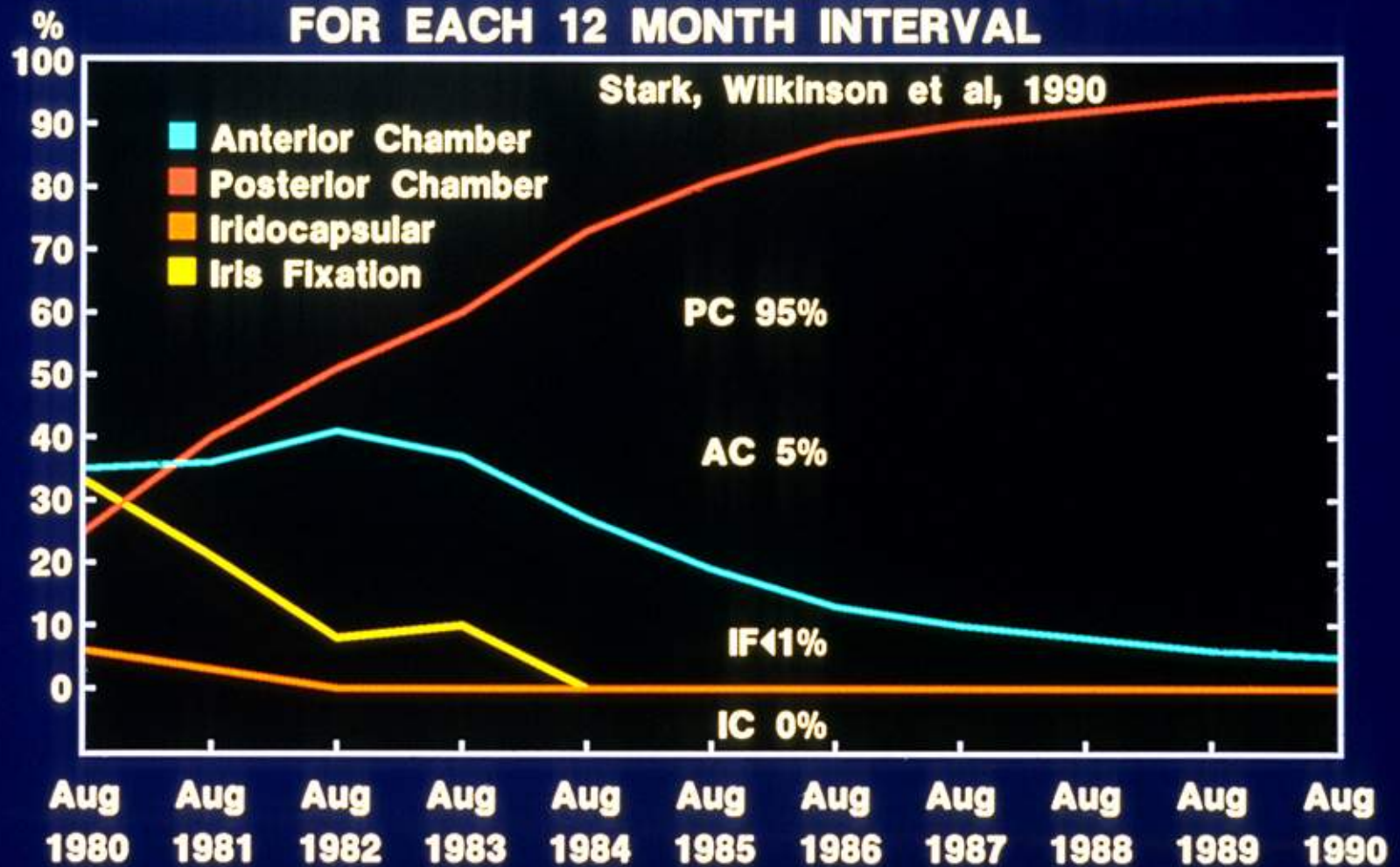


Fig 1. Number of intraocular lenses (in thousands) plotted for each six-month period since FDA study began in February 1978.

# **NUMBER OF IOLs (thousands) IMPLANTED DURING EACH 12 MONTH PERIOD**



## PERCENT OF ALL LENSES IMPLANTED BY CLASS FOR EACH 12 MONTH INTERVAL





# CORE STUDY

## SIGHT-THREATENING COMPLICATIONS(%)

### PERSISTENT AT ONE YEAR

Type of IOL	AC	IF	IC	PC
<b>N</b>	<b>5665</b>	<b>538</b>	<b>1213</b>	<b>3991</b>
<b>Macular Edema</b>	<b>2.4</b>	<b>2.4</b>	<b>0.9</b>	<b>0.8</b>
<b>Secondary Glaucoma</b>	<b>1.3</b>	<b>0.9</b>	<b>0.2</b>	<b>0.2</b>
<b>Hyphema</b>	<b>0.1</b>	<b>0.0</b>	<b>0.1</b>	<b>&lt;0.1</b>
<b>Iritis</b>	<b>1.3</b>	<b>0.9</b>	<b>0.4</b>	<b>0.7</b>
<b>Corneal Edema</b>	<b>1.2</b>	<b>1.5</b>	<b>0.6</b>	<b>0.6</b>
<b>Cyclitic Membrane</b>	<b>0.1</b>	<b>0.2</b>	<b>0.0</b>	<b>0.1</b>
<b>Vitritis</b>	<b>0.1</b>	<b>0.2</b>	<b>0.1</b>	<b>0.1</b>

# FDA Grid

- FDA updated grid in 1998, resulting in minor change
- 2001- grid incorporated into revisions of the ISO international IOL clinical investigation standards, and was renamed “Safety and Performance Endpoints.”

## Posterior chamber IOL adverse event rates

	Rate (%)
<u>Cumulative :</u>	
Endophthalmitis <sup>1</sup>	0.1
Lens dislocated from posterior chamber	0.1
Pupillary block	0.1
Hypopyon	0.3
Retinal detachment	0.3
Secondary surgical intervention <sup>2</sup>	0.8
Cystoid macular edema	3.0
<u>Persistent :</u>	
Corneal stroma edema	0.3
Iritis	0.3
Raised IOP requiring treatment	0.4
Cystoid macular edema	0.5

<sup>1</sup>Endophthalmitis is defined as inflammatory reaction (sterile or infectious) involving the vitreous body.

<sup>2</sup> Excludes posterior capsulotomies

## Anterior chamber IOL adverse event rates

Adverse event	Rate (%)
<u>Cumulative :</u>	
Hypopyon	0.2
Endophthalmitis <sup>1</sup>	0.2
Lens dislocated from anterior chamber	1.1
Retinal detachment	1.2
Pupillary block	2.0
Secondary surgical intervention <sup>2</sup>	2.6
Cystoid macular edema	10.0
<u>Persistent :</u>	
Corneal stroma edema	0.5
Iritis	0.9
Raised IOP requiring treatment	2.1
Cystoid macular edema	3.8

<sup>1</sup>Endophthalmitis is defined as inflammatory reaction (sterile or infectious) involving the vitreous body.

<sup>2</sup>Excludes posterior capsulotomies.



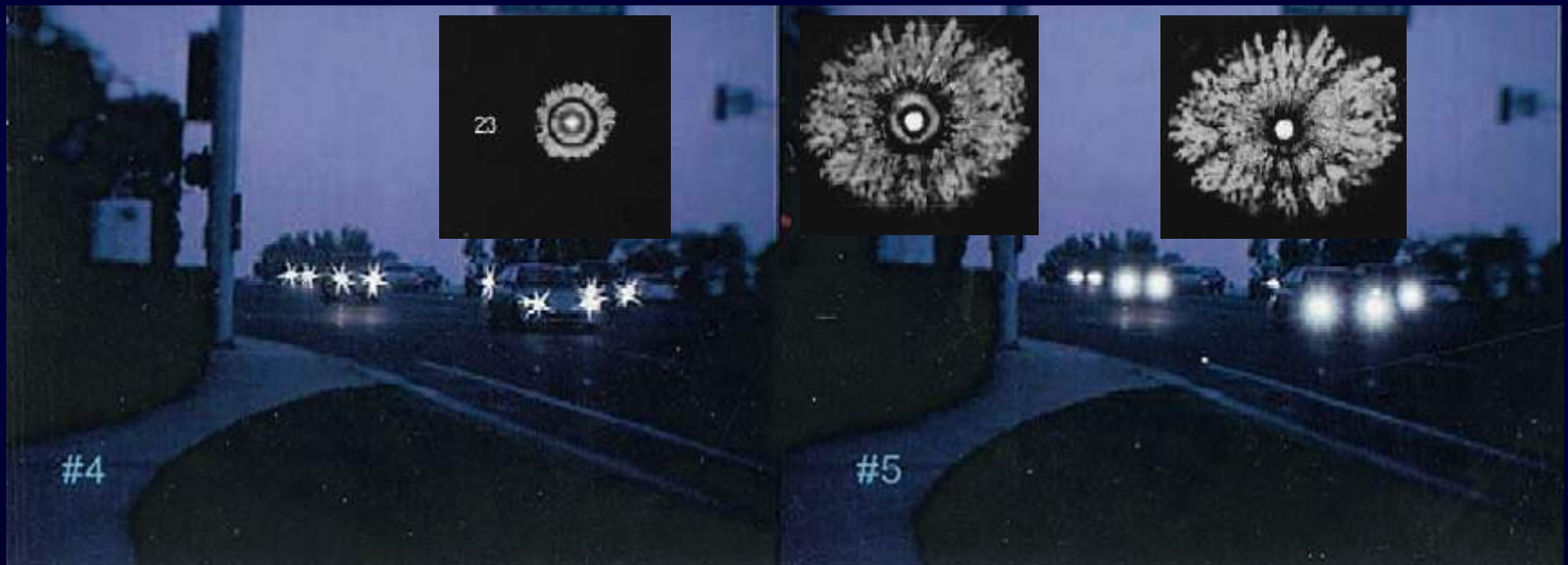
# Post-operative BCVA 0,3 logMAR or Better

Lens Type	Overall Rate %	Best Case Subject's Rate %
Anterior Chamber IOL's	80.4	90.1
Posterior Chamber IOL's	92.5	96.7

# Statements that patients say after multifocal IOL Implantation:

1. My vision is great, it is the best thing that has happened to me in years.
2. The doctor told me that I was going to have perfect vision with out glasses.
3. My vision is no better than it was; in fact, it's worse.
4. Instead of small halos around lights, I get big cob web effect around lights of oncoming cars.

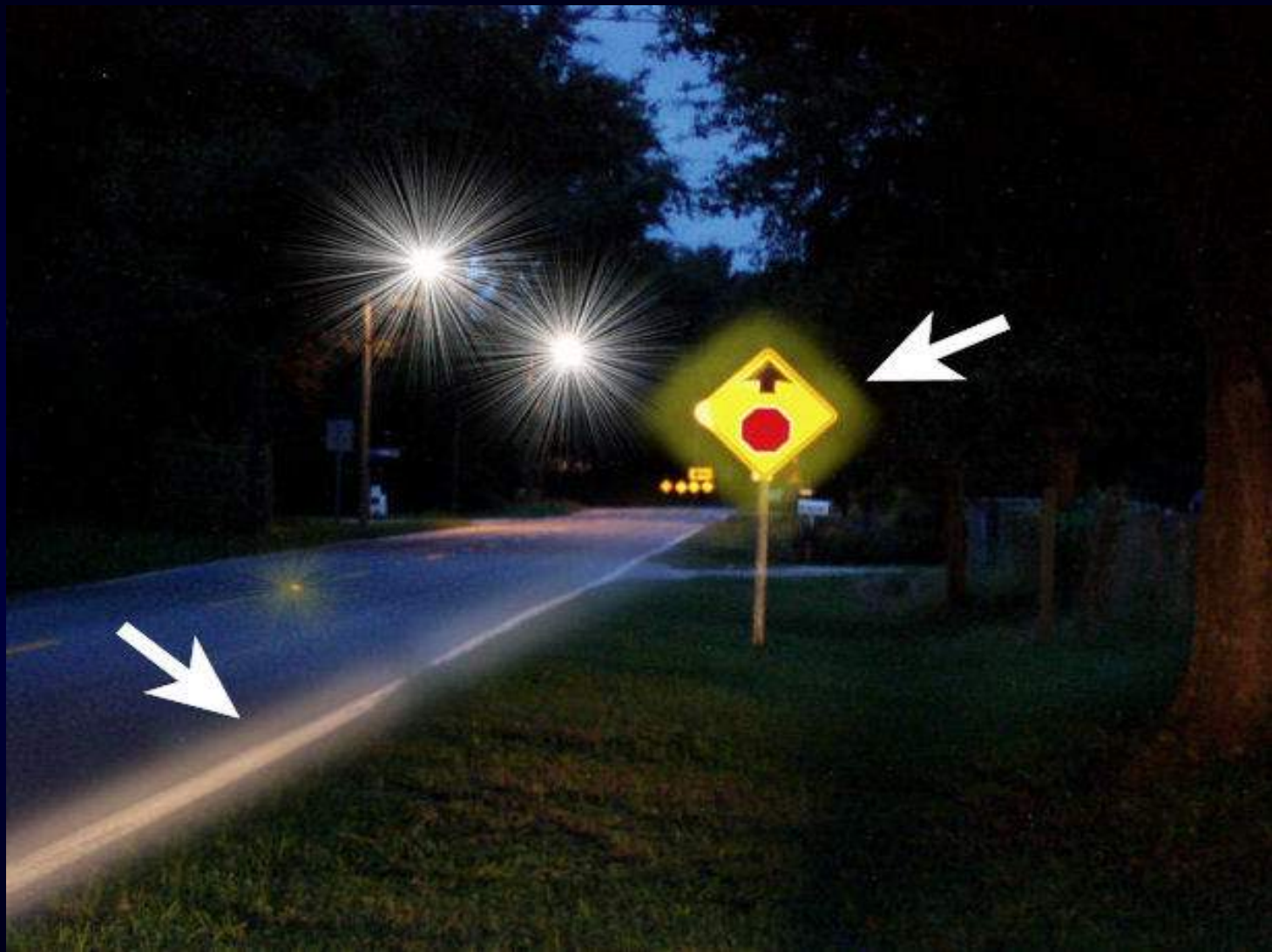
# Rings Around Lights at Night



(Hunkeler et al, J. Cat. Refr. Surg. 28:1195-1204 (2002)).

















# Comparative Nighttime Images\*

**Monofocal**



**Apodized  
Diffraction**



**Zonal Refractive  
Multifocal**

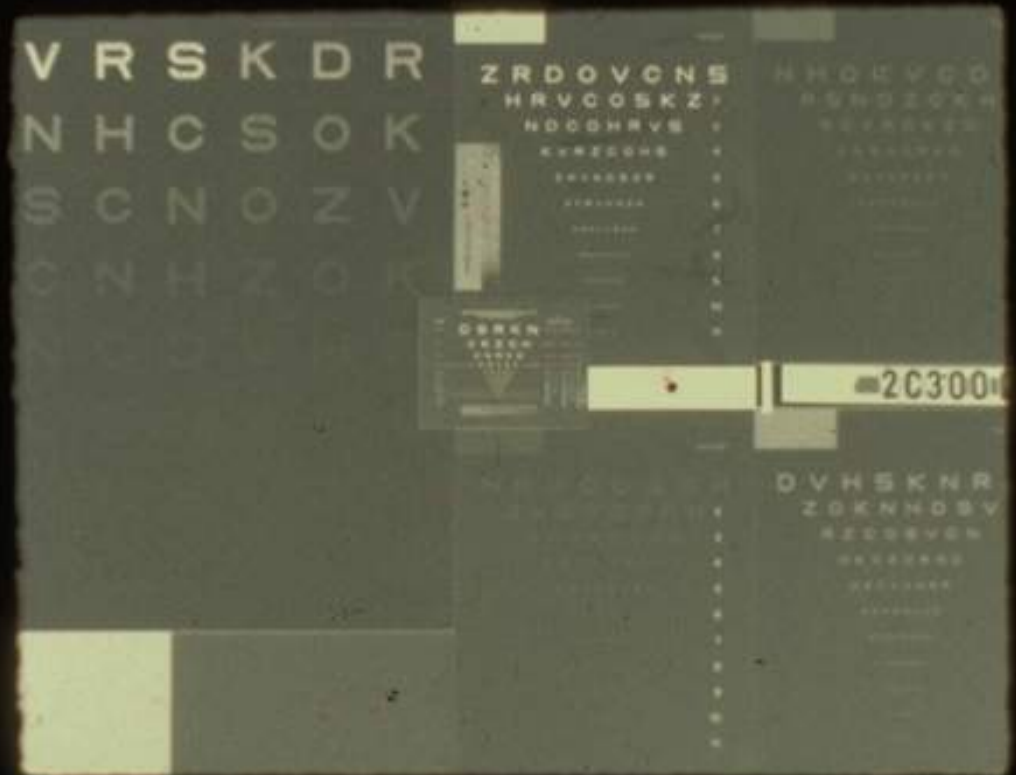


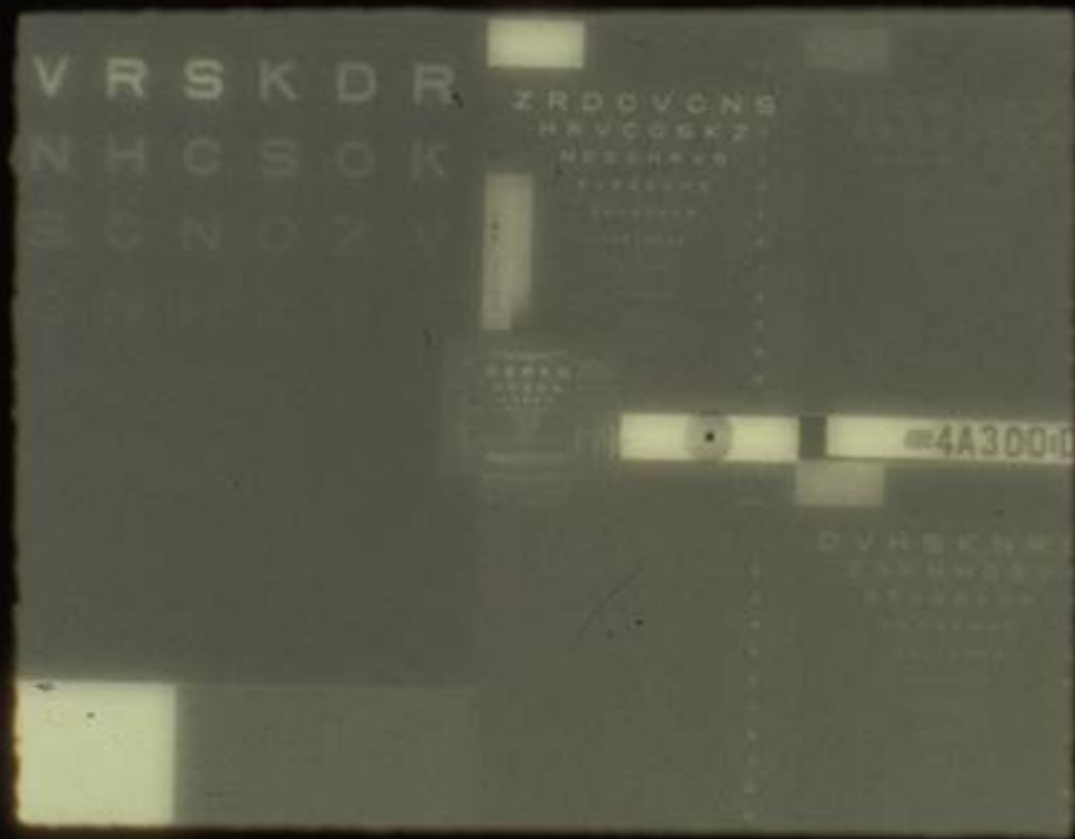
\* 5 mm Aperture, IOL in Wet Cell, simulation

# Monofocal

Distance = 20 ft.

Pupil = 3mm





Multifocal

Distance = 20 ft.

Pupil = 3mm

Figure 6  
Frequency of Spectacle Wear  
Distance Vision, Bilateral Comparison

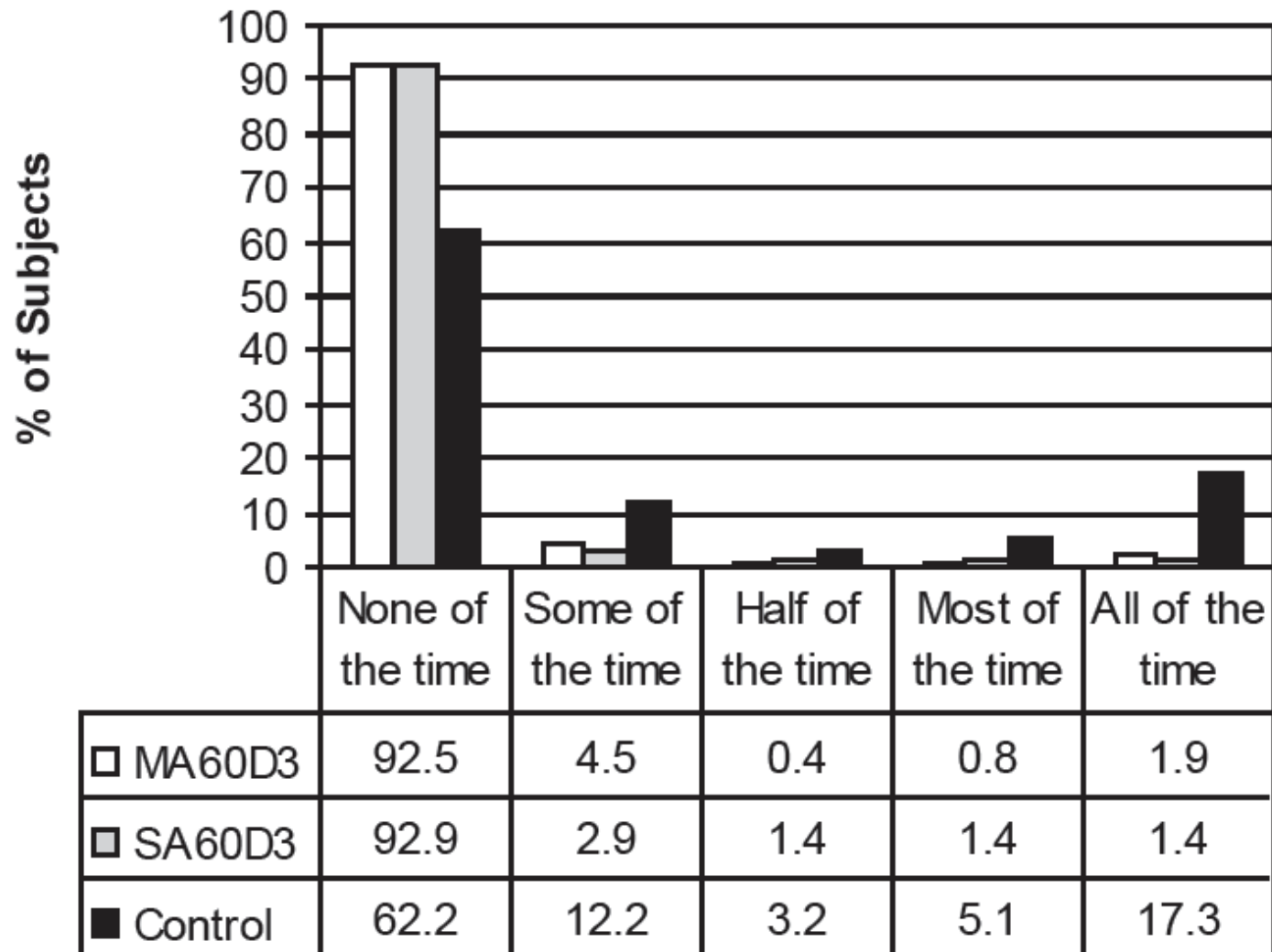


Figure 7  
Frequency of Spectacle Wear  
Near Vision, Bilateral Comparison

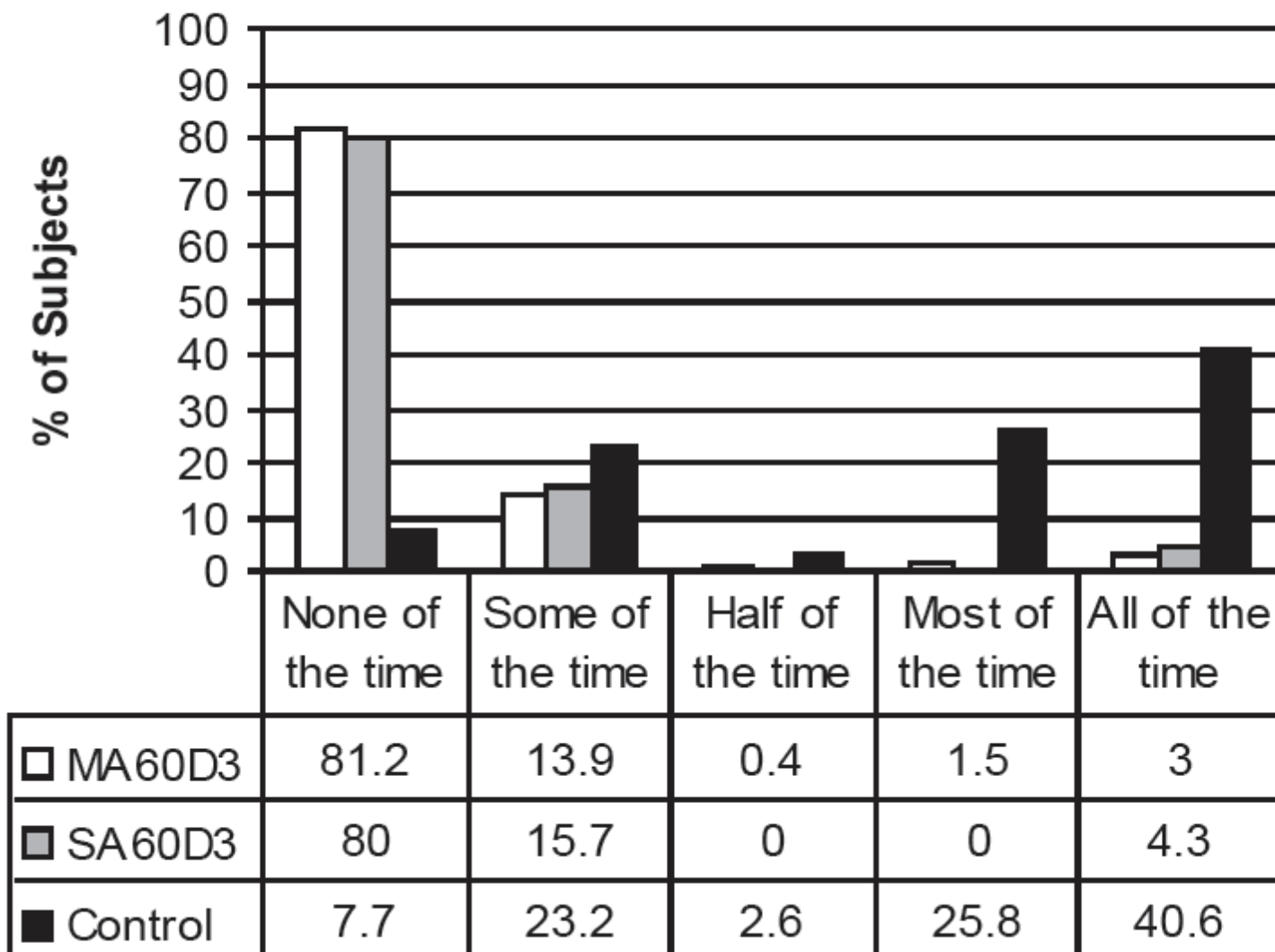




Table 18  
**ReSTOR® IOL versus FDA Historical Grid, First Eye - Safety**

	ReSTOR® MA60D3 (N=440)		ReSTOR® SA60D3 (N=126)		FDA Grid rate*
	N	%	N	%	%
Cumulative Adverse Events					
Endophthalmitis	0	0.0	0	0.0	0.1
Macular Edema	12	2.7	1	0.8	3.0
Retinal Detachment/Repair	0	0.0	1	0.8	0.3
Hyphema	0	0.0	0	0.0	2.2
Pupillary block	1	0.2	0	0.0	0.1
Lens Dislocation	0	0.0	0	0.0	0.1
Surgical reintervention	10	2.3	2	1.6	0.8
IOL replacement for biometry error	2	0.5	0	0.0	NA
IOL replacement for incorrect power/ operating room error	2	0.5	0	0.0	NA
IOL replacement for visual disturbance	1	0.2	0	0.0	NA
IOL replacement for decentered IOL due to trauma	1	0.2	0	0.0	NA
IOL replacement due to patient dissatisfaction	0	0.0	1	0.8	NA
Laser treatment	3	0.7	1	0.8	NA
Fibrin removal	1	0.2	0	0.0	NA
Persistent Adverse Events:					
Macular Edema	0	0.0	0	0.0	0.5
Raised IOP Requiring Treatment	0	0.0	0	0.0	0.4
Corneal Edema	0	0.0	0	0.0	0.3
Iritis	0	0.0	0	0.0	0.3

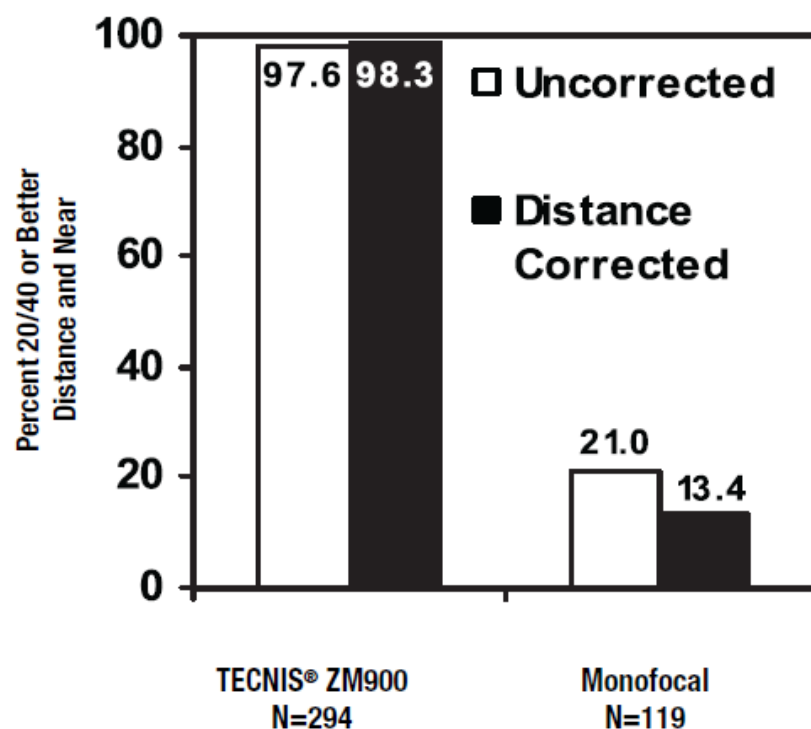
Table 19  
Visual Disturbances, 6 Months Postoperative  
(Following second eye implantation)

Visual Disturbance	ReSTOR® Model MA60D3		ReSTOR® Model SA60D3		Monofocal Control	
	% Moderate	% Severe	% Moderate	% Severe	% Moderate	% Severe
Glare/Flare	20.1	4.9	23.2	4.3	7.1	1.9
Problems with Night Vision	8.5	4.1	10.1	2.9	3.8	1.9
Halos	18.0	4.4	23.2	7.2	1.9	1.3
Distorted Near Vision	0.8	0.8	0.0	0.0	0.6	0.0
Distorted Far Vision	1.0	0.3	0.0	0.0	0.6	0.0
Blurred Near Vision	5.9	0.8	7.2	0.0	12.8	3.8
Blurred Far Vision	5.9	1.0	5.8	0.0	3.2	0.6
Double Vision in both eyes	1.5	0.8	1.4	0.0	1.3	0.0
Problems with Color Perception	0.5	0.0	0.0	0.0	0.0	0.0

Table 13  
**Sign Identification Distances in City Scene**

Identification Distance (feet)		Lens		Difference	% Loss Over Control
		Control	ReSTOR®		
Visibility Condition	Targets				
Normal	Text	160 ± 30	143 ± 31	17	10.8 %
	Warning	211 ± 26	201 ± 25	10	4.7 %
Fog	Text	159 ± 24	138 ± 34	21	13.2 %
	Warning	208 ± 23	184 ± 31	24	11.7 %
Glare	Text	142 ± 33	102 ± 46	40	28 %
	Warning	194 ± 26	170 ± 28	24	12.5 %

**Figure 1:**  
Combined 20/40 or Better Binocular Distance and Near Photopic Visual Acuity at 4-6 Months



**Figure 2:**  
Combined 20/25 or Better Binocular Distance and 20/32 or Better Binocular Near Photopic Visual Acuity at 4-6 Months

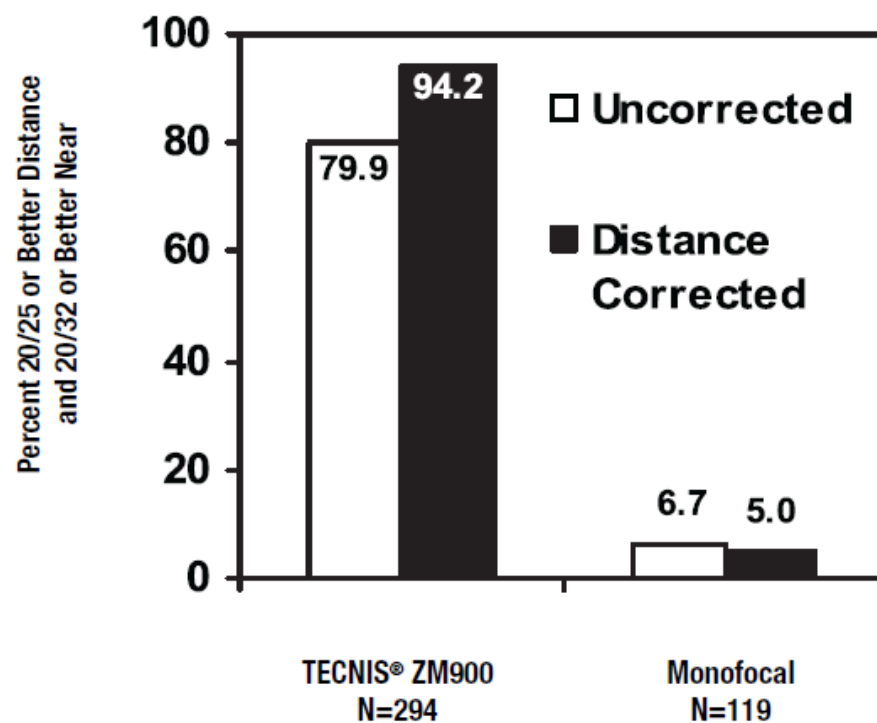
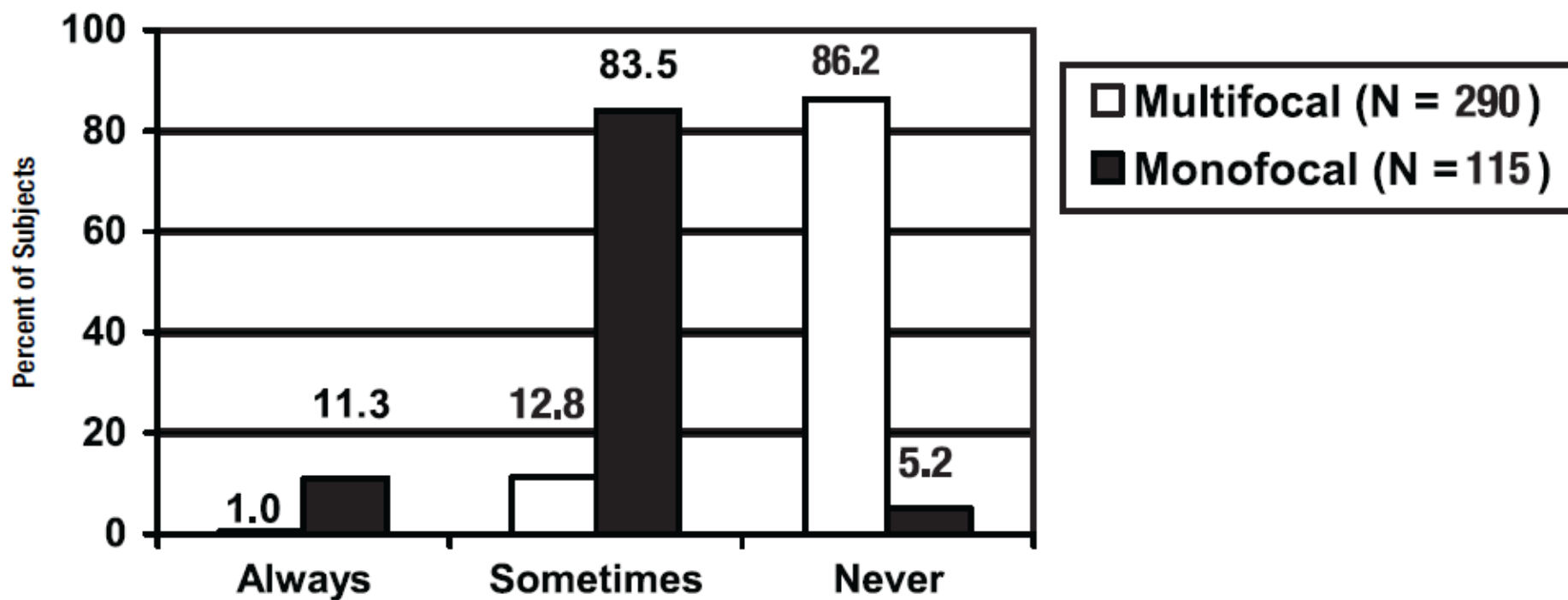


Figure 8:  
Spectacle Usage for Bilateral Subjects at One Year



**Table 17**  
**Visibility Distance and Time for City Detection**

Visibility Condition	Target	Mean Visibility Distance (feet)		Difference (feet)	Mean % Loss	Mean Visibility Time (sec)	
		ZM900	Monofocal			ZM900	Monofocal
Normal	Text	279 ± 37	333 ± 44	54	16.2%	5.43	6.48
	Warning	297 ± 31	320 ± 32	23	7.1%	5.79	6.23
	Pedestrian	348 ± 89	358 ± 92	10	2.6%	6.78	6.97
Fog	Text	255 ± 49	300 ± 41	45	15.0%	4.97	5.85
	Warning	276 ± 28	303 ± 30	27	9.0%	5.37	5.90
	Pedestrian	326 ± 80	358 ± 88	32	8.9%	6.36	6.98
Glare	Text	229 ± 42	279 ± 32	50	17.8%	4.46	5.43
	Warning	266 ± 32	295 ± 32	29	9.9%	5.17	5.74
	Pedestrian	291 ± 69	326 ± 82	35	10.7%	5.66	6.35



**Table 18**  
**Visibility Distance and Time for City Identification**

Visibility Condition	Target	Mean Visibility Distance (feet)		Difference (feet)	Mean % Loss	Mean Visibility Time (sec)	
		ZM900	Monofocal			ZM900	Monofocal
Normal	Text	255 ± 30	312 ± 37	57	18.3%	4.96	6.07
	Warning	293 ± 33	320 ± 32	27	8.4%	5.70	6.23
	Pedestrian	324 ± 72	348 ± 82	24	7.1%	6.31	6.79
Fog	Text	219 ± 40	273 ± 32	54	19.7%	4.27	5.32
	Warning	269 ± 32	300 ± 30	31	10.2%	5.25	5.85
	Pedestrian	305 ± 65	343 ± 71	38	11.0%	5.95	6.68
Glare	Text	199 ± 57	263 ± 39	64	24.3%	3.88	5.12
	Warning	261 ± 35	293 ± 31	32	11.1%	5.08	5.71
	Pedestrian	276 ± 53	310 ± 65	34	10.9%	5.38	6.04

## for First Eyes, Non-directed Responses at 4-6 Months and One Year

Optical/Visual Symptoms	TECNIS® ZM900		Monofocal Control	
	4-6 Months N=333	One Year N=331	4-6 Months N=119	One Year N=116
<b>Visual Disturbances</b>				
Day glare	3.9%	6.0%	1.7%	1.7%
Floaters	4.2%	5.7%	4.2%	2.6%
Halos <sup>#</sup>	<b>40.8%</b> Mild = 16.5% Moderate = 15.3% Severe = 9.0%	<b>24.5%</b> Mild = 12.7% Moderate = 6.3% Severe = 5.4%	<b>4.2%</b> Mild = 2.5% Moderate = 1.7%	<b>8.6%</b> Mild = 6.0% Moderate = 2.6%
Night glare <sup>#</sup>	<b>14.1%</b> Mild = 5.1% Moderate = 5.4% Severe = 3.6%	<b>11.8%</b> Mild = 3.3% Moderate = 5.7% Severe = 2.4%	<b>4.2%</b> Mild = 2.5% Moderate = 1.7%	<b>4.3%</b> Mild = 1.7% Moderate = 0.9% Severe = 1.7%
Starburst <sup>#</sup>	<b>8.1%</b> Mild = 3.6% Moderate = 3.3% Severe = 1.2%	<b>6.3%</b> Mild = 2.4% Moderate = 2.1% Severe = 1.8%	<b>0.8%</b> Mild = 0.8%	<b>1.7%</b> Mild = 1.7%
Night vision difficulty	3.3%	1.5%	0.0%	0.0%
Entoptic phenomena <sup>†</sup>	4.2%	2.1%	1.7%	1.7%
Other image quality <sup>‡</sup>		1.8%		0.9%
<b>Image Quality</b>	<b>19.5%</b> Overall = 3.3% Distance = 5.4% Intermediate = 11.1% Near = 2.4%	<b>18.4%</b> Overall = 2.4% Distance = 5.7% Intermediate = 8.2% Near = 2.7%	<b>14.3%</b> Overall = 4.2% Distance = 0.0% Intermediate = 0.8% Near = 9.2%	<b>12.9%</b> Overall = 2.6% Distance = 1.7% Intermediate = 0.9% Near = 7.8%
Blurred/difficulty with vision				
Cloudy/hazy/filmy/foggy vision	3.9%	5.4%	1.7%	2.6%
Decreased vision	3.9%	4.5%	1.7%	2.6%
Fluctuation in acuity	3.6%	3.0%	5.9%	2.6%

**Table 24**  
**Cumulative Adverse Events for TECNIS® ZM900 First Eyes**

Cumulative Adverse Event	ZM900 N=348*		FDA Grid Rate
	n	%	%
Hyphema	0	0.0	2.2
Macular edema	9	2.6	3.0
Retinal detachment	0	0.0	0.3
Pupillary block	0	0.0	0.1
Lens dislocation	0	0.0	0.1
Endophthalmitis	1 <sup>#</sup>	0.3	0.1
Hypopyon	1 <sup>#</sup>	0.3	0.3
Surgical re-intervention	13	3.7	0.8
Lens-related	2 <sup>‡</sup>	0.6	
Not lens-related	11 <sup>#</sup>	3.2	

t with lens exchange due to incorrect lens type included in study population for adverse events only.  
 nced endophthalmitis and hypopyon followed by non-lens-related surgical re-interventions (trabecu

ects experienced lens-related events during the study (0.9%; 3/348); however only two of these ex  
 completion, two of the three subjects experienced lens-related events in the first eye (one of whi

**Table 5**  
**Bilateral Distance Corrected Near Visual Acuity (1 Year Versus 3 Year)**

	<b>1 Year</b>		<b>3 Year</b>	
20/25 or better	64/124	51.6%	29/50	58.0%
20/32 or better	104/124	83.9%	42/50	84.0%
20/40 or better	124/124	100%	50/50	100%
Worse than 20/40	0/124	0%	0/50	0%

**Table 8**  
**Bilateral Patient Survey**  
**Difficulty With Night Activity**  
**US Bilateral Subjects**

<b>Symptoms</b>	<b>Absent N/N (%)</b>	<b>Mild N/N (%)</b>	<b>Moderate <u>n/N (%)</u></b>	<b>Severe <u>n/N (%)</u></b>
Night-time glare/flare	74/130 (56.9%)	31/130 (23.8%)	18/130 (13.8%)	7/130 (5.4%)
Night vision (difficulty driving at night)	82/121 (67.8%)	21/121 (17.4%)	14/121 (11.6%)	4/121 (3.3%)
Halos (rings around lights)	80/130 (61.5%)	26/130 (20.0%)	16/130 (12.3%)	8/130 (6.2%)

**Table 10**  
**Adverse Events Reported at 12 months**

Adverse Event	Cumulative		FDA Grid	Persistent		FDA Grid
	Primary Eyes	All Eyes		Primary Eyes	All Eyes	
Endophthalmitis	1/324 (0.3%)	1/497 (0.2%)	0.1%	----	----	----
Hyphema	1/324 (0.3%)	1/497 (0.2%)	2.2%	----	----	----
<u>Hypopyon</u>	0/324	0/497	0.3%	----	----	----
IOL Dislocation	0/324	0/497	0.1%	----	----	----
Cystoid Macular Edema	12/324 (3.7%)	13/497 (2.6%)	3.0%	2/304 (0.7%)	3/450 (0.7%)	0.5%
Pupillary Block	0/324	0/497	0.1%	----	----	----
Retinal Detachment	0/324	0/497	0.3%	----	----	----
<u>Secondary Surgical Reintervention</u>	2/324 (0.6%)	4/497 (0.8%)	0.8%	----	----	----
Corneal Edema	----	----		0/298	0/440	0.3%
<u>Iritis</u>	----	----		2/298 (0.7%)	3/440 (0.7%)	0.3%
Raised IOP Requiring Treatment	----	----		0/304	0/450	0.4%



# Influence of Multifocal Intraocular Lenses on Standard Automated Perimetry Test Results

Nancy Aychoua, MD; Francisco G. Junoy Montolio, MD; Nomdo M. Jansonius, MD, PhD

**Importance:** A multifocal intraocular lens (MFIOL) allows for spectacle independence after cataract surgery and is thus a seemingly attractive option. However, several optical limitations have been reported or

**Main Outcome Measures:** Primary outcome measures were the mean deviation (MD) for size III and the mean sensitivity (MS) for size V. Comparisons between groups were adjusted for age and pupil size.

**Results:** For SAP size III, the average difference in MD between patients in the MFIOL group and phakic controls was  $-2.40$  dB ( $P < .001$ ) and between patients in the monofocal IOL group and phakic controls was  $-0.32$  dB ( $P = .52$ ).

**Participants:** Sixteen eyes of 16 patients with a diffractive MFIOL (median age, 64 years), 18 phakic eyes of 18 healthy individuals serving as controls (median age, 62 years), and 12 eyes of 12 patients with a monofocal IOL (median age, 64 years) were included.

**Interventions:** All participants underwent (1) SAP using a 30-2 grid and the Swedish Interactive Threshold Algorithm standard strategy with stimulus size III and (2) a full threshold test with stimulus size V.

Visual sensitivity was assessed with both size III and size V. The reduction seems to be related to the multifocal design of the IOL rather than to pseudophakia. The reduction interferes with the assessment of common eye diseases such as glaucoma and comes on top of the decline of visual sensitivity due to normal aging or age-related eye diseases, thus potentially accelerating visual impairment.

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Published online February 21, 2013.

doi:10.1001/jamaophthalmol.2013.2368

# Safety and Performance Endpoints: Summary

Used by FDA, Ophthalmic Devices Panel and  
manufacturers as a historical control

Need to be updated to accommodate newly  
designed IOL's

- Posterior capsule clouding-need for YAG laser
- Night time glare and halos
- Sign identification distance-% loss over control
- Secondary surgical intervention
- Pupillary Block glaucoma (AC and phakic IOL's)
- Better inform patients as to risks
- Proper patient selection